DETAILED ACTION

Amendment and Status of the Claims

Applicant's amendment filed 6/19/09 is acknowledged and entered.

Claims 20-21, and 38-56 are presently pending.

Claims 1-19, 22-37, and 57 have been canceled.

Claims 20-21, 38-41 and 56 have been previously withdrawn and remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 42-55 are under consideration.

Sequence Rules Compliance

The sequence rules have apparently been complied in view of the amendment to the specification filed 6/19/09.

Drawings

The amended drawings filed 6/19/09 are acknowledged and accepted.

Specification

The objection to the specification set forth in the previous Office action has been withdrawn in view of the amendment to the specification filed 6/19/09.

Claim Rejections-35 USC § 112

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-55 are rejected under 35 U.S.C. 112 , second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 42 is amended to recite "mutagenizing a Staphylococcus genome with a transposon such that individual cells containing at least one transposon insertion site are isolated." The metes and bounds of the limitation are unclear because it is not clear whether it means each of the individual cells, where the individual cells are interpreted to mean a group of cells, contains at least one transposon insertion site, or the entire group of cells contain at least one transposon insertion site.

Furthermore, it is unclear as to the metes and bounds of the limitation "transposon insertion site." On the one hand, it could mean the site or location in a genome where a transposon is to be inserted. On the other hand, it could also mean the site or location in a genome where a transposon has been inserted. Consequently, the metes and bounds of the HTTIM database are unclear because it is not clear whether the polynucleotide sequences of the insertion sites comprise the sequences of the transposons.

The phrase "said database of transposon insertion sites" in step c) of claim 42 lacks antecedent basis because there is only a prior reference to a database of polynucleotide sequences of the transposons, not the database of the transposons, per se.

Claim 42 is also amended to recite "a database comprising the Staphylococcus genome…." The metes and bounds of the limitation are unclear because it is not clear as

to what exactly are comprised in the database. A genome of an organism would be reasonably understood by one skilled in the art to mean the entire physical genomic DNA of the organism. It is thus unclear what is meant by a database comprising a genome because a database cannot comprise physical DNA molecules. The genome could be represented by its entire sequence, its genetic maps, its physical maps, etc. Therefore, even if applicant meant to indicate the database comprises a representation of the genome, it would still be unclear as to what is meant: the entire genomic sequence, or maps, or else.

The phrase "said putative essential or important genes that are not disrupted by a transposon" in step d) of claim 42 lacks clear antecedent basis because there is prior reference in the steps to "putative essential or important genes that are not disrupted by a transposon."

Applicant's arguments filed 6/19/09 have been fully considered but they are moot as the above rejections are for reasons necessitated by applicant's amendment.

Clarification of the metes and bounds of the claims is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Charles et al. (IDS document: WO 01/07651 A2, 1 February 2001) in view of Haselbeck et al. (IDS document: WO 01/70955 A2, 27 September 2001).

In view of the indefiniteness of the claims as set forth above, the references cited are being applied to the best interpretation of the claims as currently written.

The claims are drawn to a method for identifying a library of putative essential or important genes using a High Throughput Transposon Insertion Database (HTTIM), comprising: mutagenizing a Staphylococcus genome with a transposon such that individual cells containing at least one transposon insertion are isolated; collecting and

mapping the polynucleotide sequences of the transposon insertion sites in each individual cell so as to form a database of polynucleotide sequences of the transposon insertion sites, or an HTTIM; comparing said database of polynucleotide sequences of transposon insertion sites with a database comprising the Staphylococcus genome to identify open reading frames in the genome that are not disrupted by a transposon insertion; and forming a library from said putative essential or important genes that are not disrupted by a transposon.

Charles et al. disclose a method for making a library of putative essential genes comprising mutagenizing bacterial cells such as Staphylococcus genome with transposon to obtain a library of mutants; and isolating polynucleotide sequences from the library which flank the inserted transposon sites to obtain a pool of consensus probes. These steps are interpreted as the "mutagenizing" and the "collecting" steps recited in the instant claims. The method of Charles et al. also includes hybridizing the consensus probes with a polynucleotide library from the same organism, and identifying nucleotide sequences in the library to which the consensus probe sequences do not hybridize, which are putative essential genes of the organism. See at least pages 2 and 6-7. Since the consensus sequences are those flanking the transposons, they represent those genes that are disrupted by the transposons. Those sequences from the library that are identified as not being hybridized to the consensus sequences are those genes that are not disrupted by any transposons. Charles et al. also disclose that ideally the hybridization is done with the library in the form of a gridded array that represents the whole genome of the organism and each location represents a single open reading frame. When the entire genomic sequence is known, the order of all the open reading frames is known and the transposon

sites are thus mapped by the hybridization. See at least pages 13-14. This hybridization step is interpreted as comparing a pool of sequences of the insertion sites (interpreted as a file of sequences of insertion sites) with a library of genomic sequences of the organism.

Charles et al. do not explicitly disclose comparing a database of polynucleotide sequences of transposon insertion sites with a database comprising the genomic sequence of the organism. However, Charles et al. do teach the use of bioinformatics tools to allow rapid isolation of further essential genes by searching databases of known genomic sequences to isolate orthologous genes, etc. See page 17.

Haselbeck et al. disclose a method for identifying putative essential genes by using antisense sequences. The method comprises identifying nucleotide sequences from the inserts of vectors that represent sequences of genes affecting proliferation and growth, comparing the sequences with know genomic sequences of the organism in databases such as GenBank, TIGR databases and the Pathoseq database to identify open reading frames that comprise these sequences, which are genes affecting proliferation and growth. See at least pages 94-96.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the way of comparing isolated sequences with known databases containing entire genomic sequences and/or all open reading frames to identify genes or open reading frames as disclosed by Haselbeck et al., would be much more advantageous, such as time saving, than the physical hybridization method as disclosed by Charles et al. Furthermore, one of ordinary skill in the art would have understood that the physical hybridization between two sequences would conceivably be considered as comparison between the two sequences because the result of the hybridization, i.e. sequences that

match and mismatch would be similar to the result of a comparison, i.e. an alignment showing sequences that match and mismatch. Therefore, one of ordinary skill in the art at the time of the instant invention was made would have been motivated to modify the method of Charles et al. to applying the method of comparing a database of sequences of insertion sites with a database containing the entire genomic sequence and all the open reading frames of the organism to take advantage of the latter method such as to save time.

With regard to claims 45-50, which specify the approximate numbers of transposons in the mutant library and number of genes in the library of putative essential genes, it would have been obvious to one of ordinary skill in the art that the number of transposons in the mutant library and the number of essential genes as disclosed by Charles would vary depending on the scale and exhaustiveness of the particular experiment and the genome size of the organisms up to the maximum number of essential genes, and the extend of the identification. Charles et al. encourage combining two transposon libraries thereby increasing the probability of obtaining transposon insertions in a greater number of genes. See page 9. It would have been obvious that one could obtain any number of transposons or genes in the library as desired.

With regard to claim 51, which recite statistical calculations, given that Charles et al. and Haselbeck et al. teach of using bioinformatics tools including searching databases of GenBank etc. using BLAST and database comparison, it would have been readily apparent that certain statistical calculations such as probability would be applied.

With regard to claims 53-55, which recite verifying the essential genes, Charles et al. disclose a method of such verification involving creating promoter swap mutants. See pages 16-17.

Special Notes from the Examiner

The method claims are interpreted to have a physical transformation because the steps of "mutagenizing" and "collecting" are construed as physical steps of inserting transposons into the genome by an experimental procedure that transformed at least a bacterial genome without the transposon into a genome with the transposon inserted into various sites therein, and it is construed that no embodiment of the claimed invention includes an in silico step of "mutagenizing" and "collecting." Because of this, no rejection under 35 USC 101 (patent subject matter eligibility) is made.

Applicant's arguments filed 6/19/09 have been fully considered but not persuasive. Applicant argues that the cited references do not teach or suggest collecting and mapping polynucleotide sequences of the transposon insertion sites. See page 17 of 18 of the response, the second full paragraph. This is not found persuasive because as set forth in the previous Office action and reiterated above, Charles et al. disclose mutagenizing bacterial cells such as Staphylococcus genome with transposon to obtain a library of mutants and isolating polynucleotide sequences from the library which flank the inserted transposon sites to obtain a pool of consensus probes. The method of Charles et al. also includes hybridizing the consensus probes with a polynucleotide library from the same organism, and identifying nucleotide sequences in the library to which the consensus probe sequences do not hybridize, which are putative essential genes of the

organism. See at least pages 2 and 6-7. This clearly indicates that the polynucleotide sequences of the insertion sites are collected and mapped.

Applicant further argues that nowhere does the primary reference Charles et al. suggest sequencing transposon insertion sites. See page 17 of 18 of the response, the third full paragraph. This is not found persuasive because Charles et al. on page 2, lines 16-17, explicitly disclose isolating polynucleotide sequences from the library which flank the inserted transposons. Given the indefiniteness of the limitation of polynucleotide sequences of the transposon insertion sites of the instant claims for reasons set forth above in the section of rejection under 35 USC 112, second paragraph, this collection of polynucleotide sequences flanking the inserted transposons by Charles et al. are interpreted as the polynucleotide sequences of the transposon insertion sites of the instant claims.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. §1.136 (a). A shortened statutory period for response to this final action is set to expire three months from the date of this action. In the event a first response is filed within two months of the mailing date of this final action and the advisory action is not mailed until after the end of the three-month shortened statutory period, then the shortened statutory

period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. §1.136 (a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than six months from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran, can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Shubo (Joe) Zhou/

SHUBO (JOE) ZHOU, PH.D.

PRIMARY EXAMINER